## REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the amendments above and comments below.

Claims 20-24 are pending in the subject application.

The specification has been amended to provide SEQ ID NOs. for disclosed nucleic acid sequences. A computer readable copy and hard copy of a Sequence List are enclosed herewith. The hard copy and computer disc are identical and contain the same information. No new matter is added by the filing of the Sequence List. It is respectfully requested that the enclosed sequence list be entered in the subject application.

### I. Objections to the Specification and Claims

It is respectfully submitted that the amendments to the specification to add sequence identifiers and to enter a Sequence List render the objection to the specification moot. The amendments to claims 20 and 23 render the objection to these claims moot.

### II. Rejection of Claims 20-24 Under 35 U.S.C. § 112, First Paragraph

The Examiner states that the specification does not reasonably provide an enabling disclosure for a method of treating thyroid cancer by inducing the re-expression of the human sodium/iodide symporter in a human thyroid carcinoma cell *in vivo*. The Examiner also asserts that the five cited prior art references support a conclusion that the claimed method does not work *in vivo* because the agents used are toxic and/or mutagenic.

Applicants respectfully disagree with the Examiner's conclusions.

The present invention is directed to methods of inducing re-expression of a sodium/iodide symporter gene in thyroid carcinoma cells *in vivo* by administering an effective amount of a

compound selected from the group set forth in claim 20. The listed compounds are unblocking agents that effect induction *via* demethylation or differentiation. Applicants' studies have demonstrated that administration of these agents to thyroid carcinoma cells restores iodide uptake in the cells.

On page 3 of the Office Action the Examiner states that the observation that thyroid carcinoma cells transcribe the sodium-iodide symporter is consistent with the interpretation that those carcinoma cells are more differentiated than thyroid carcinoma cells that do not express the sodium-iodide transporter. The Examiner also asserts that the induction of differentiation of cancer cells is considered a target of cancer research, but that the agents employed in the present invention are cytotoxic and non-specific. Finally, the Examiner cites to a number of references as demonstrating the toxicity and/or mutagenic effects of the agents used in the present invention and concludes that the prior art teaches that the claimed invention cannot be used to treat cancer.

Applicants respectfully disagree with the examiner's conclusions.

Turning to the Examiner's comments concerning the state of differentiation of thyroid carcinoma cells that have lost the sodium-iodide symported function, it is not clear what the Examiner's point is. The fact of the matter is that dedifferentiation of cancer cells is most often disconjugate, with the loss of some functions and retention of others. Thus, one cannot conclude that loss of sodium-iodide transport is indicative of the degree of dedifferentiation of the cells. (See K.Ain, Balliere's Clinical Endocrinol. And Metab., (2000) 14(4):615-629, copy enclosed).

Moreover, the present invention is not directed to methods of inducing differentiation of thyroid carcinoma cells, but instead is directed to methods of maintaining and inducing a single differentiated function of these cells- the ability to effectively transport iodide. It is an object of the present invention to reverse an epigenetic event in the carcinoma cell, that is, to induce the

expression of the genes involved in sodium-iodide transport, which are inactive in thyroid carcinoma cells due to methylation thereof. Applicants' data clearly demonstrate that the agents employed in the present invention effectively decrease methylation and restore iodide transport in thyroid carcinoma cells (See page 16 of the specification, for example).

The Examiner relies on several references as teaching that the recited agents are cytotoxic or as teaching that use of such agents leads to mutations or metastasis. However, this is a gross oversimplification of these references. For example, Carr et al, which the Examiner relies on as teaching that 5-aza-cytidine is ineffective for treatment of small-lung carcinoma and causes a multitude of undesirable effects, did not even use 5-aza-cytidine. Instead, these researchers tested 5,6-dihydro-5-azacytidine, which is distinct compound and is not used in the present invention. Moreover, the effect of 5-azacytidine on small lung carcinoma cells is not at issue. The present invention is directed to treatment of thyroid cancer, and specifically at methods of inducing sodium-iodide transport in these cells. Sodium-iodide transport is not an issue in small lung cell carcinoma.

The Examiner also states that Bender et al. conclude that demethylating agents should be developed that are more specific than 5-azacytidine. That notwithstanding, Bender et al. demonstrated that 5-azacytidine is effective in treating specified cancers and suggests "that demethylating agents may have long-term therapeutic effects on patients." This reference also teaches that since 5-azacytidine is effective in the treatment of leukemia, it should be studied for treatment of specific types of cancer, rather than used universally, since it has known toxic side effects. That is precisely what the claimed invention does.

Thomas et al. is also relied on by the Examiner as teaching that mice treated with 5-azacytidine develop tumors. However, the mice treated in the Thomas et al. study were on long-

term gointrogen treatment, which is not a part of the present invention. Thus, this reference is mischaracterized and irrelevant to the present invention.

The Examiner further relies on Hancock et al. and Takenaga et al. as supporting a conclusion of ineffectiveness and toxicity of 5-azacytodine in the treatment of thyroid carcinoma. However, neither article draws such a conclusion. Hancock et al. conclude that "Demethylation of DNA, which is the most likely effect of treatment with 5-azacytidine, could provide a rapidly alterable means to express some transformation-associated phenotypes." (p. 838) Takenaga et al., who studied the effects of highly polar compounds on cloned Lewis lung carcinoma cell metatstasis, limited their studies to *in vitro* analysis of cloned cells, and did not draw the conclusions proffered by the Examiner. Takenaga et al.'s studies were aimed at determining the factors responsible for attachment and adhesion of cancer cells *in vitro* , and do not support a conclusion that polar compounds such as DMSO cause metatstasis.

Thus, the cited prior art does not lead to a conclusion that the claimed invention is not effective and is, instead, toxic. To that end, Applicant submits herein five references that teach the use of 5-azacytidine to treat various disorders, such as experimentally induced anemia in baboons resulting from an inactive gamma gene (Heller et al., copy enclosed); sickle cell anemia in humans (Charache et al. and Dover et al., copies enclosed); beta-thalassemia in humans (Ley et al., copy enclosed). In each reference, patients were treated *in vivo* with 5-azacytidine at a level that did not produce life threatening side effects and each case, the induction of gene expression was observed. Thus, contrary to the Examiner's assertions, the prior art supports the *in vivo* effectiveness of the claimed methods, and together with the data in the specification provides evidence that the claimed invention is enabled.

It is respectfully submitted that the rejection of claims 20-24 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

Accordingly, it is submitted that the present application is in condition for allowance, an early notification thereof being earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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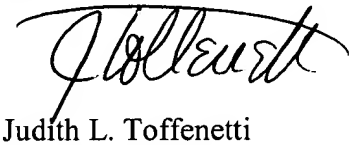

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